REMARK

Reconsideration of the present application is respectfully requested.

Status of the Claims

Claims 1, 9, 10, and 12 remain pending, and claim 12 was withdrawn for being directed to non-elected subject matter.

Claim Rejections-35 USC 103

Claims 1, 9 and 10 stand rejected under 35 USC 103(a) as allegedly being unpatentable over SHUBER, KMIEC, ALBERTSON, and BUCK. This rejection is respectfully traversed.

The Declaration previously filed was not considered sufficient to overcome the rejection. The position maintained was that the data obtained with the claimed primers compared to "new" primers are neither unexpected nor superior.

However, applicant respectfully submits the following three key facts:

1. The data reported in Table 1 indicates that the two sets of primers, albeit located in close regions of the target sequences, determine significantly different results in terms of FL-DNA, as evidenced by the sample concordance correlation coefficient pc=0.0456.

2. The different quantitative PCR readouts observed with the two sets of primers determine unexpected results in terms of accuracy to detect colorectal cancer. Table 2 shows that at the same cut-off, the differences in terms of sensitivity and specificity are relevant and unexpected. In fact, the purpose of this test is to detect colorectal Cancer patients. The higher sensitivity of the claimed primers is not balanced by the lower specificity at cut-offs of 20-30 ng, as alleged in the Official Action. The specificity still remains over 80%, only 10-20% lower than the specificity obtained by new primers, conversely the sensitivity was 50% or higher. In an early diagnosis program, higher sensitivity is more important than specificity if one considers that false positive results would make necessary further diagnostic tests as the only consequence, whereas false negative results may have serious, negative consequences for the patient health.

3. Contrary to the assertions made on page 4 -lines 1-4 of the Office Action, the "new" primers are optimized for PCR amplification. Instead, they are not "optimized" for cancer detection - at least, they are not as much as the claimed primers - and there is no suggestion in the prior art to modify such primers for obtaining a valuable patient-discrimination ability using a quantitative PCR analysis.

Furthermore, the Official Action contends that the optimization of amplification through selection of primer sequences was taught by SHUBER. However, the claimed invention is a method for the diagnosis of colorectal tumor, not a method of PCR amplification/detection. It is important to understand that the effectiveness of the claimed method is measured in terms of ability to detect colorectal tumor patients vs. non-tumor individuals; the *"optimization of amplification through selection of primer sequences and other factors"* (Office Action, page 4, last par.) is not the aim of the invention. Whereas it might be conceded that SHUBER and BUCK teach to select primers in order to optimize sequencing of the target DNA, they are completely silent about quantification of the target DNA by means of a PCR technique based on primers labeled with fluorescent markers, as in the claimed invention.

To make this concept clear, the "claimed" and "new" primers reported in the Declaration may well give comparable PCR amplification efficiencies, but they differ substantially when compared for their ability to discriminate among colorectal tumor patients and non-tumor individuals, using a quantitative PCR-based method of diagnosis of colorectal tumors as in the claimed invention. The selection of primers that allow a better detection of colorectal tumor patients, as opposed to a better amplification or sequencing of the target DNA, is not suggested by SHUBER, BUCK or KMIEC.

This achievement is unexpected considering that there is no direct correlation between the sensitivity of an amplification technique and the efficacy of a screening method, as it is possible that a more accurate or sensitive amplification method results in a substantially identical or even worse capability of differentiating between affected and unaffected individuals. The two aspects must be kept separate, because a more sensitive detection of amplicons may only show a higher level of DNA without discriminating between the two groups of individuals.

Therefore, it is respectfully maintained that the claimed method is unobvious and provides unexpected superior results to those suggested by the proposed combination.

Improper Information Disclosure

As requested, the Official Action an Information Disclosure Statement is being submitted with documents discussed in the previous Amendment. These documents were discussed as further evidence of the unexpected results of the claimed invention, as they exemplify the knowledge of one of ordinary skill in the art. For example, the quality and quantity of genomic DNA that can be extracted from stool as claimed was previously considered poor (International Journal of Cancer); the analysis method of SHUBER is different and does not give the same results as those obtained by the claimed invention (Neoplasia); and the ethidium bromide used by SHUBER is probably the least effective

reagent for this type of analysis (Cancer Research, Analytical Biochemistry, and PCR Methods and Applications). Consideration of these documents in their entirety for the reasons explained in the Amendment of February 16, 2010 is respectfully requested.

Conclusion

In view of the foregoing remarks, this application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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